Diffusion Primer

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1. What is Diffusion?

Diffusion is one of several "transport processes" that occur in nature. A distinguishing feature of diffusion is that it results in mixing or mass transport without requiring bulk motion. Thus, diffusion should not be confused with convection or dispersion, which are other transport mechanisms that use bulk motion to move particles from one place to another.

2. Gedanken Experiment

Paul Berg's book "Random Walks in Biology" (1), describes a useful thought experiment that illustrates the diffusion phenomenon. Imagine carefully introducing a drop of colored fluorescent dye into a jar of water. Initially, the dye remains concentrated at the point of release, but over time, it spreads radially, in a spherically symmetric distribution. This mixing process is taking place without stirring or other "convective" processes.

3. Underlying Physical Process

This diffusive mixing results solely from collisions between molecules in liquids and gases. Another interesting feature of diffusion is that it occurs even in thermodynamic equilibrium. For example, it can occur in a jar of water kept at a constant temperature and pressure. This is quite remarkable, because the classical picture of diffusion, expressed in Fick's First Law (2,3) was that, particles, like heat, flow from regions of high concentration to low concentation. When these gradients vanished, however, there was no net flux. There were many who held that diffusion stopped at this point. While the net flux vanishes, however, there are still diffusive fluxes nonetheless, however they cancel each other.

4. Brownian Motion

Robert Brown is credited with being the first one to discover random motions of pollen grains while studying them through his microscope (4). It wasn't until Einstein revisited this phenomenon in the early 20^{th} century that a coherent description of diffusion emerged, identifying the diffusion coefficient in Fick's law and the variance of the particle displacement distribution that describes the migration of particles in "Brownian motion".

5. Einstein's insights into the diffusion process

Einstein was able to derive an explicit relationship between the mean-squared displacement of a particle and the classical diffusion coefficient (5,6). Langevin improved Einstein's description of diffusion for ultra-short timescales in which there are few molecular collisions.

Since collision times in typical solvents like water are about 0.1 nanoseconds, we generally do not concern ourselves with this correction in NMR experiments.

6. Edwin Hahn

Hahn realized that the spin echoes he discovered were sensitive to the effects of diffusion. He reported the reduction of signal of the spin echo and explained it in terms of the dephasing caused by translational diffusion of spins subjected to local magnetic field gradients due to inhomogenities in the magnetic field (7).

7. Carr and Purcell

Carr and Purcell (8), building on the observations of Hahn, showed that NMR spin echoes could be sensitized to diffusion in a way that permits its direct measurement. They proposed using a Hahn spin echo experiment in which constant gradients were applied throughout the pulse sequence. During the first period (between the 90º and 180º pulses), molecules would dephase at different rates depending on the instantaneous position within the gradient field, acquiring some net phase. During the second period (between the 180º pulse and the echo) spins would refocus at different rates depending on their position in the gradient field. If particles were stationary or moving at the same constant speed, the echo magnitude would be unchanged in this experiment. However, if particles were diffusing throughout the experiment, the phase increment gained during the first period would not generally cancel the phase accrued during the second period, resulting in phase dispersion among the population of spins and an overall loss of signal intensity, which was ascribed directly to diffusion. Carr and Purcell proposed NMR sequences to sensitize the NMR spin echo to the effects of diffusion, and developed a mathematical framework to measure the diffusion coefficient from such sequences.

8. Stejskal and Tanner

Stejskal and Tanner (9) introduced many innovations that made modern diffusion measurements by NMR and MRI possible. First, they introduced the Pulsed Gradient Spin Echo (PGSE) sequence, which replaced Carr and Purcell's constant gradients with short duration gradient pulses. This allowed a clear distinction between the encoding time (pulse duration) and the diffusion time. They also provided a solution to the Bloch-Torrey equations that included diffusion as a relaxation process (10), specifically showing how the magnitude and phase of the NMR signal is related to diffusivity. Stejskal and Tanner also solved the Bloch-Torrey equation (9) for the case of free, anisotropic diffusion in the principal frame of reference. However, the Stejskal –Tanner formula is not generally useable to measure an effective diffusion tensor using NMR or MRI methods for several reasons: First, this formula relates a time-dependent diffusion tensor, to the NMR signal, so one must define a relationship between the time-dependent diffusion tensor and an effective diffusion tensor. Second, in the pre-MRI era (in which the Stejskal-Tanner formula was derived) it was always tacitly assumed that a homogeneous anisotropic sample could be physically reoriented within the magnet so that its principal axes could be aligned with the axes of the laboratory coordinate frame. After the development of MRI, however, this assumption was no longer tenable. Materials under study (like tissue) were often heterogeneous optically turbid media whose principal axes were generally not known *a priori* and could vary from region to region within the sample. Thus, a general scheme had to be developed to measure the entire diffusion tensor (both its diagonal and off-diagonal elements) in

each voxel within the laboratory frame of reference (11). Stejskal and Tanner also proposed a general Fourier relationship for the PGSE experiment between the measured signal and the displacement distribution, which laid the foundation for subsequent developments of q-space NMR and MRI (12,13).

9. What is Diffusion Anisotropy?

In tissues, such as brain gray matter, where the measured apparent diffusivity is largely independent of the orientation of the tissue (i.e. isotropic) at the voxel length scale; it is usually sufficient to describe the diffusion characteristics with a single (scalar) apparent diffusion coefficient (ADC). However, in anisotropic media, such as skeletal and cardiac muscle (14) (15), (16) and in white matter (17) (18) (19) where the measured diffusivity is known to depend upon the orientation of the tissue, a single ADC can not characterize the orientation-dependent water mobility. The next most complex model that can describe anisotropic diffusion replaces the scalar diffusion coefficient with a symmetric effective or apparent diffusion *tensor* of water, $\underline{D}$ (e.g., see (20)).

10. What Causes Diffusion Anisotropy in Tissues?

The causes of diffusion anisotropy have not been fully elucidated in brain parenchyma, although most investigators ascribe it to ordered, heterogeneous structures, such as large oriented extracellular and intracellular macromolecules, supermacromolecular structures, organelles, and membranes. Clearly, in the central nervous system (CNS), diffusion anisotropy is not simply caused by myelin in white matter, since several studies have shown that even before myelin is deposited, diffusion anisotropy can be measured using MRI (21) (22-24). Thus, despite the fact that increases in myelin are temporally correlated with increases in diffusion anisotropy, structures other than the myelin sheath must significantly contribute to diffusion anisotropy (25). This is important because the degree of diffusion anisotropy is not a quantitative measure or "stain" of myelin content (26).

11. Concluding Remarks:

As water (or another spin-labeled molecule) undergoes diffusion, it also encounters barriers, macromolecules, sampling many different local environments. Collectively, the signal we measure in an NMR experiment contains contributions from water motion in these various microenvironments. The challenge in diffusion NMR and MRI is to try to back off or infer features of the local tissue anatomy, composition and microstructure from displacement measurements. One great advantage of MR is that it permits one to probe tissue structure at different length scales—i.e., levels of architectural organization. Specifically, while the mean-squared displacement of water is on the order of microns for typical MR experiments, these molecular motions are ensemble-averaged within a voxel, and then subsequently assembled into multi-slice or 3-D images of tissues and organs. Thus, this imaging modality permits us to study and elucidate complex structural features spanning length scales ranging from the macromolecular to the macroscopic – without the use of exogenous contrast agents.

12. Bibliography:

1. Berg HC, editor. Random Walks in Biology. Princeton, N.J.: Princeton University Press; 1983.
2. Fick A. Concerns diffusion and concentration gradient. Ann Phys Lpz 1855;170:59.
3. Fick A. Über Diffusion. Ann Phys 1855;94:59.
4. Brown R. On the general existence of active molecules in organic and inorganic bodies. Philos Mag, Ann Philos 1828;New Series, 4.
5. Einstein A. Über die von der molekularkinetischen Theorie der Wärme geforderte Bewegung von in ruhenden Flüssigkeiten suspendierten Teilchen. Annalen der Physik 1905;17:549-560.
6. Einstein A. Investigations on the theory of the Brownian movement. New York: Dover Publications, Inc.; 1926. 119 p.
7. Hahn EL. Spin-echoes. Phys Rev 1950;80(4):580-594.
8. Carr HY, Purcell EM. Effects of diffusion on free precession in nuclear magnetic resonance experiments. Phys Rev 1954;94(3):630-638.
9. Stejskal EO, Tanner JE. Spin diffusion measurements: spin echoes in the presence of time-dependent field gradient. Journal of Chemical Physics 1965;42(1):288-292.
10. Torrey HC. Bloch equations with diffusion terms. Physical Review 1956;104(3):563-565.
11. Basser PJ, Mattiello J, Le Bihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. J Magn Reson 1994;B 103(3):247-254.
12. Callaghan PT. Principles of nuclear magnetic resonance microscopy. Oxford: Oxford University Press; 1991.
13. Cory DG, Garroway AN. Measurement of translational displacement probabilities by NMR: an indicator of compartmentation. Magn Reson Med 1990;14(3):435-444.
14. Cleveland GG, Chang DC, Hazlewood CF, Rorschach HE. Nuclear magnetic resonance measurement of skeletal muscle: anisotropy of the diffusion coefficient of the intracellular water. Biophys J 1976;16(9):1043-1053.
15. Garrido L, Wedeen VJ, Kwong KK, Spencer UM, Kantor HL. Anisotropy of water diffusion in the myocardium of the rat. Circ Res 1994;74(5):789-793.
16. Tanner JE. Self-diffusion of water in frog muscle. Biophys J 1979;28(1):107-116.
17. Henkelman RM, Stanisz GJ, Kim JK, Bronskill MJ. Anisotropy of NMR properties of tissues. Magn Reson Med 1994;32(5):592-601.
18. Moseley ME, Cohen Y, Kucharczyk J, Mintorovitch J, Asgari HS, Wendland MF, Tsuruda J, Norman D. Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. Radiology 1990;176(2):439-445.
19. Moseley ME, Kucharczyk J, Asgari HS, Norman D. Anisotropy in diffusion-weighted MRI. Magn Reson Med 1991;19(2):321-326.
20. Crank J. The mathematics of diffusion. Oxford, England: Oxford University Press; 1975. 414 p.
21. Neil JJ, Shiran SI, McKinstry RC, Schefft GL, Snyder AZ, Almli CR, Akbudak E, Aronovitz JA, Miller JP, Lee BC, Conturo TE. Normal brain in human newborns: apparent diffusion coefficient and diffusion anisotropy measured by using diffusion tensor MR imaging. Radiology 1998;209(1):57-66.
22. Beaulieu C, Allen PS. Water diffusion in the giant axon of the squid: implications for diffusion-weighted MRI of the nervous system. Magn Reson Med 1994;32(5):579-583.
23. Beaulieu C, Allen PS. Determinants of anisotropic water diffusion in nerves. Magn Reson Med 1994;31(4):394-400.

24. Wimberger DM, Roberts TP, Barkovich AJ, Prayer LM, Moseley ME, Kucharczyk J. Identification of premyelination by diffusion-weighted MRI. J Comput Assist Tomogr 1995;19(1):28-33.
25. Le Bihan D, Turner R, Douek P. Is water diffusion restricted in human brain white matter? An echo-planar NMR imaging study. Neuroreport 1993;47:887-890.
26. Pierpaoli C, Basser PJ. Toward a quantitative assessment of diffusion anisotropy [published erratum appears in Magn Reson Med 1997 Jun;37(6):972]. Magn Reson Med 1996;36(6):893-906.